Exhibit L
Part 3 of 3

correctly identifying the proper isomer in the pro-AI-2 signal blend, resulting in an advantageous gene regulation response.

Sorting and responding to pro-AI-2 may occur by mechanisms similar to those used by other biological kingdoms. Only a narrow window of signal concentration may elicit a response, as has been found for insect pheromones released and received by members of the order Lepidoptera (130, 131). Coevolution of emitters and receivers of insect pheromones occurs, and communication between the correct males and females must happen in a background of many signals specific for other species. Too much or too little pheromone elicits no response by the potential mate. Too constant an emission gets no response. Pheromones may be of the same general chemical structures but in different blends, which are specific for the correct mating. By having several chemicals in the blend, the combinations of the chemicals can yield an almost unlimited variety of blends, and each species of Lepidoptera may emit and respond to only one blend. In a similar way, the combinations of pro-AI-2 molecules formed by members of a bacterial community may be sorted and received uniquely for each species within a mixed-species community such as dental plaque.

Other factors in a microenvironment may modulate the detection and response to a blend of pro-AI-2 signals. As has been reported for distinct pH gradients caused by juxtapositioning of a variety of species (150), other chemical or physical gradients may form with certain adjacent species in a microenvironment. These conditions may influence the production of pro-AI-2 or the blend of pro-AI-2 in the extracellular pool. For example, in *S. enterica* serovar Typhimurium, increased AI-2 production occurs in high-osmolarity and low-pH environments, and a protein synthesis-dependent degradation of the signal occurs in low-osmolarity conditions (139). A prominent role for acidic environments has long been known in dental plaque, where acid-producing bacteria cause caries and consequently pose a constant threat to oral health. The acidic microenvironment present in dental plaque may be essential for proper response to chemical communication with AI-2. The physical attachment of cells of different species may cause contact-induced gene regulation, perhaps in all coaggregating cells, and result in altered production of and response to a mixture of pro-AI-2 molecules.

No matter what mechanism mixed-species communities use for AI-2 signaling, progress in understanding the role of AI-2 in complex microbial communities will come when experiments are conducted with mixed-species communities.

DIRECT-CONTACT SIGNAL: ANTIGENS I AND II

The antigen I/II (Ag I/II) family of surface proteins is represented on many species of human oral streptococci (Table 1). They contain the LPXTG motif recognized by gram-positive sortase enzymes, which tether this class of proteins to the peptidoglycan layer (47, 135). These large polypeptides range from about 1,450 to 1,570 amino acid residues and possess seven discrete, well-conserved structural domains. These multifunctional proteins bind to other bacteria, host tissue, salivary conditioning film on teeth, and soluble molecules. Thus, the Ag I/II polypeptides are excellent candidates for mediating the adherence of streptococci to surfaces and providing an opportunity to communicate with other residents of the environment. A complete description of these properties and the immunogenicity of the proteins is found in two reviews (66, 67). Some of the recent progress in defining a role for Ag I/II proteins in promoting the dominance of streptococci in dental plaque will be discussed here.

TABLE 1. Ag I/II homologues of oral streptococci

Organism	Protein(s)	Reference(s)
S. constellatus	—[a]	24, 99
S. cricetus	PAa	144
S. gordonii	SspA, SspB	37
S. intermedius	—	24, 124
S. mitis	—	23
S. mutans	SpaP, Pac, Protein I/IIf	71, 116
S. oralis	—	16
S. sobrinus	SpaA, PAg	85, 146

[a] —, homologue with no designation.

Considering that Ag I/II proteins on different streptococcal species contain well-conserved structural domains, it is not surprising that they also exhibit overlapping functions, such as binding to human salivary glycoproteins. However, they do possess specific functions as well, which arise from the activity of distinct structural domains. Small changes in the primary sequence can have profound changes in the functional character of Ag I/II proteins. For example, in SspB, an Ag I/II homologue in *S. gordonii*, a region spanning residues 1167 to 1250 is required for adherence to a coaggregation partner, *P. gingivalis* (13). Changing two residues, Asn^{1182} to Gly and Val^{1185} to Pro, yields a protein predicted to possess secondary structure similar to that of SpaP, an Ag I/II homologue in *S. mutans*, which does not coaggregate with *P. gingivalis*. Recombinant strains of *S. gordonii* bearing the modified proteins lost the ability to coaggregate with *P. gingivalis* (38), confirming that this region of these two homologues differs functionally as well as structurally.

In contrast, an example of functional similarity is that the Ag I/II proteins of both *S. mutans* and *S. gordonii* bind to human collagen type I, a major component of dentin, and facilitate invasion of human root dentinal tubules by these species (95). Testing the multifunctional capabilities of SspB was accomplished by comparing the abilities of *S. gordonii* and *S. mutans* to bind to human collagen type I and to coaggregate with *P. gingivalis*. Both abilities were required for *Streptococcus-Porphyromonas* coinvasion of dentinal tubules (96). *P. gingivalis* was able to invade dentinal tubules when cocultured with *S. gordonii* bearing SspA and SspB. An *S. gordonii sspA/B* mutant deficient in collagen binding did not support coinvasion with *P. gingivalis*; *S. mutans* bearing SpaP invaded human root dentinal tubules but did not support coinvasion with *P. gingivalis*. The results of these studies illustrate discrete functions embodied within the Ag I/II structures and the relevance of surface adhesins to the colonization of indigenous environments by bacteria.

Another discrete function of Ag I/II proteins is the ability to mediate coaggregation with actinomyces partner cells. *S. gordonii* strains DL1 and M5 each have two Ag I/II paralogs, SspA and SspB, which are involved in coaggregation with *A. naeslundii*. The genes encoding these proteins are arranged in tandem on the chromosomes of these strains and, in strain DL1, are

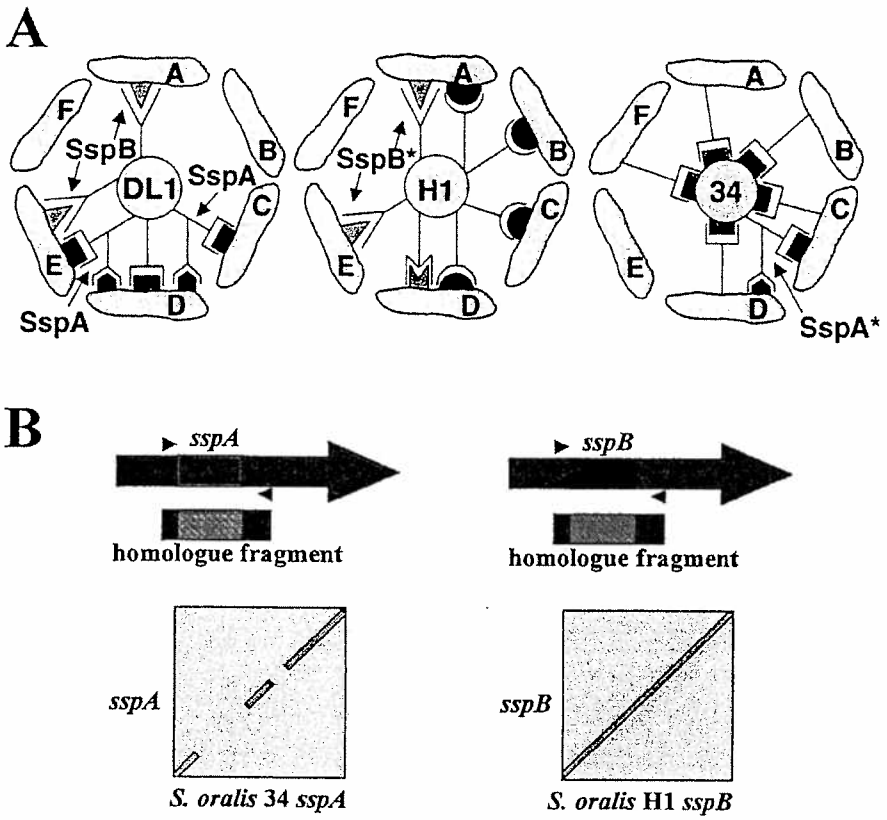

FIG. 6. (A) Involvement of Ag I/II family members in *Streptococcus-Actinomyces* coaggregations. The diagram shows coaggregations between *S. gordonii* DL1, *S. oralis* H1, and *S. oralis* 34 (representatives of streptococcal coaggregation groups 1, 2, and 3, respectively) with six actinomyces coaggregation groups (groups A, B, C, D, E, and F) (72). Actinomyces coaggregation groups are symbolized by oblong cellular shapes containing letters representing the groups and surround the three circles representing streptococcal strains DL1, H1, and 34. The model of *S. gordonii* DL1 coaggregation is based on identification of the independent coaggregation functions of SspA and SspB of *S. gordonii* DL1 (41). The models for *S. oralis* strains H1 and 34 are based on pairwise coaggregations between actinomyces and streptococci, lactose-inhibitable coaggregations, and loss of certain coaggregation functions by spontaneous mutants (72). The complementary symbols shown here are described in the legend to Fig. 1. *, putative protein designations. (B) Graphic representation of *sspA* and *sspB* (accession number U40027), with divergent regions shown in green and purple and gene fragments amplified from *S. oralis* 34 and *S. oralis* H1 encoding Ag I/II homologues. The locations of primers (solid arrowheads) used to amplify the homologous fragments from *S. oralis* H1 (purple-stippled rectangle) and *S. oralis* 34 (green-stippled rectangle) are shown. Blast2 alignments (145), shown below, reveal that the divergent regions of *S. gordonii sspB* and the *S. oralis* H1 homologue are conserved over the length of this region (conserved sequences appear as a straight line at a 45° angle). However, alignment of the *sspA* divergent region and the corresponding region from the *S. oralis* 34 homologue reveals gaps in the sequence identity. The similarities and differences in these sequences may be responsible for the coaggregations with *A. naeslundii* strains shown in panel A. See text for more detail.

known to exhibit different patterns of regulation in response to environmental conditions (43). Furthermore, it appears that *sspB* transcription is positively regulated by the *sspA* gene product, suggesting an additional role for SspA (42).

Earlier surveys of coaggregations between streptococci and actinomyces yielded six coaggregation groups of actinomyces, representing the range of coaggregations observed with approximately 90% of the 300 human oral *A. naeslundii* strains tested (41, 73). Recent results focused on *S. gordonii* DL1 have shown that SspA and SspB are adhesins critical for coaggregation with four of the six actinomyces coaggregation groups (41) (Fig. 6A). Others have shown that inactivation of *sspA* of *S. gordonii* DL1 resulted in a loss of greater than 50% of the wild-type ability to coaggregate with *A. naeslundii* T14V (coaggregation group A) and *A. naeslundii* PK606 (coaggregation group D) (68).

Construction of *sspB* insertion mutants of both *S. gordonii* DL1, and an isogenic *sspA* mutant allowed the first study of the independent functions of SspA and SspB (41). SspA exhibited two coaggregation-specific functions; it participated in lactose-inhibitable and lactose-noninhibitable interactions (Fig. 6A, cognate symbols complementary to red rectangle and red obelisk, respectively). Mutation of *sspA* resulted in changes in coaggregation with three of the four actinomyces coaggregation groups. For example, the *sspA* mutant was unable to coaggregate with actinomyces coaggregation group C (Fig. 6A). SspB mediated only lactose-noninhibitable coaggregations (Fig. 6A, cognate symbol complementary to yellow-green tri-

angle). The *sspB* mutant was unable to coaggregate with actinomyces coaggregation group A, and its coaggregation with actinomyces coaggregation group E was changed from lactose noninhibitable to lactose inhibitable. A change from lactose noninhibitable to lactose inhibitable is possible because the former coaggregation masks the latter in the presence of lactose. The effects of the mutations were additive in the *sspAB* double mutant; however, it retained a single previously unrecognized lactose-inhibitable coaggregation with *A. naeslundii* PK606 (coaggregation group D) (Fig. 6A, cognate symbol complementary to gray rectangle). Thus, SspA and SspB appear to mediate all coaggregations between *S. gordonii* DL1 and the actinomyces coaggregation groups except the lactose-inhibitable coaggregation with actinomyces coaggregation group D.

SspA and SspB show a high level of sequence identity in *S. gordonii* strains M5 and DL1 (37). The complete sequences of *sspA* and *sspB* from *S. gordonii* DL1 have recently been determined (accession number U40027). Comparison of the C-terminal half of the deduced sequences of SspA and SspB shows that they are 98% identical, and the sequences of the N-terminal third of the polypeptides are 96% identical. The intervening divergent regions are only 37% identical. Comparison of these sequences to the corresponding sequences of strain M5 indicates 93% identity between the SspA sequences and 95% identity between the SspB sequences. Thus, the genetic organization of these two genes as well as the sequence similarity both between the paralogs in strains M5 and DL1 and between the orthologs of strains M5 and DL1 indicate close relationships.

This broad range of functions attributed to SspA and SspB suggested that perhaps other streptococci might also employ one or both of these proteins in mediating coaggregations with actinomyces. Two examples are depicted along with the coaggregation model of *S. gordonii* DL1 with the six actinomyces coaggregation groups A to F (Fig. 6A). Both *S. oralis* H1 and *S. oralis* 34 express a surface protein that cross-reacts with antiserum (gift of D. Demuth) recognizing both SspA and SspB. However, *S. oralis* H1 and *S. oralis* 34 exhibit patterns of coaggregation with actinomyces that are distinct from that of *S. gordonii* DL1 (Fig. 6A).

By using primers designed to hybridize with conserved sequence flanking the divergent region of both *sspA* and *sspB* of *S. gordonii* DL1, genomic DNA from *S. oralis* strains H1 and 34 was used as the template to PCR amplify the divergent region of the Ag I/II genes from these strains (Fig. 6B). Sequence analysis of the resultant PCR products revealed that the *S. oralis* 34 divergent region was 86% identical to *sspA*, while the *S. oralis* H1 divergent region was 93% identical to the corresponding region of *sspB*. Alignment (145) of the divergent region and short flanking conserved regions of *S. gordonii* DL1 *sspA* with the *sspA* homologue fragment from *S. oralis* 34 shows large gaps in sequence identity (Fig. 6B, left graph). In comparison, alignment of the *sspB* homologue fragment from *S. oralis* H1 with *S. gordonii* DL1 *sspB* contains no gaps (Fig. 6B, right graph).

Considering this identity of *S. gordonii* DL1 *sspB* and the *S. oralis* H1 homologue, it is not surprising that both *S. gordonii* DL1 and *S. oralis* H1 exhibit the same SspB-mediated interactions with actinomyces (Fig. 6A, left and center, respectively). Accordingly, comparison of streptococci bearing the less similar SspA homologues revealed distinct coaggregation patterns in *S. gordonii* DL1 and *S. oralis* 34 (Fig. 6A, left and right, respectively). Apparently, changes predicted in the *S. oralis* 34 SspA homologue are sufficient to prevent recognition of the lactose-sensitive receptor on actinomyces coaggregation group E. Examination of SspA and SspB homologues in these streptococcal strains indicates that these proteins are integral to the adherence abilities of oral streptococci and are structurally and functionally distinct.

Besides mediating adherence to actinomyces, these two surface proteins bind salivary agglutinin glycoprotein (36, 68). This may represent one of the many mechanisms that streptococci employ to adhere to salivary conditioning film on enamel surfaces. The outcome of *S. gordonii* DL1 binding to saliva was investigated by random arbitrarily primed PCR. Such studies showed that exposure of *S. gordonii* DL1 to saliva resulted in induction of *sspA/B* expression (39). Thus, bathing cells of *S. gordonii* DL1 in saliva, a condition expected to occur in the oral cavity, causes them to synthesize surface adhesins that bind salivary receptors. One hypothesis is that such binding would encourage removal of the streptococcal cells by agglutination and swallowing. Another hypothesis is that such binding promotes attachment to surfaces through salivary receptor bridging between SspA/B-bearing planktonic cells and already attached bacteria. In fact, coating streptococci with saliva may enhance binding to surfaces and prevent disappearance from the mouth by swallowing.

Consistent with the second hypothesis, we have shown that suspending streptococci in saliva does not reduce their ability to coaggregate with actinomyces (81) or with other streptococci (78). Also, our results with streptococci and actinomyces growing in biofilms on saliva-conditioned glass surfaces with saliva as the sole nutrient source indicate that these bacteria adhere and grow luxuriantly (120). Presumably, the ability to communicate under these conditions is enhanced by being coated with saliva, because the habitat in which these bacteria coevolved with their host is bathed in saliva.

FUTURE DIRECTIONS

In plaque, as in most natural biofilm ecosystems, spatial heterogeneity exists with respect to species location in the axial and lateral dimensions (see Fig. 2); the spatial organization changes with time as a result of interspecies communication and gene expression. Elucidating the architecture of dental plaque at the species level is possible with the use of confocal microscopy coupled with appropriate probes based on 16S rDNA sequences and antibodies that recognize cell surface epitopes of oral bacteria. Probe specificity can be tested in biofilm models in vitro. Temporal dental plaque studies can be conducted in situ. The development of fluorescence-based reporters that function in an anaerobic environment needs to be encouraged. When these probes become available, they will promote study of gene regulation in anaerobic periodontal biofilm communities that include human oral spirochetes. Gene regulation induced by cell-cell contact is underinvestigated; the development of reporters based on green fluorescent protein will facilitate future studies. Current approaches such as in vivo expression technology, DNA microarrays, and

proteomics provide the platforms for large-scale analysis of gene expression.

The genomes of *F. nucleatum* (70), *S. mutans* (B. A. Roe, R. Y. Tian, H. G. Jia, Y. D. Qian, S. P. Lin, S. Li, S. Kenton, H. Lai, J. D. White, R. E. McLaughlin, M. McShan, D. Ajdic, and J. Ferretti, *Streptococcus mutans* Genome Sequencing Project, 26 March 2002 posting date; www.genome.ou.edu/smutans.html), *P. gingivalis* (http://www.tigr.org), and *A. actinomycetemcomitans* (B. A. Roe, F. Z. Najar, S. Clifton, T. Ducey, L. Lewis, and S. W. Dyer, *Actinobacillus* Genome Sequencing Project, 26 March 2002 posting date; www.genome.ou.edu/act.html) have been sequenced, and at least 10 other oral bacterial genomes are being sequenced. Investigation in silico will offer great opportunity to identify specific genes hypothesized to be relevant to intraspecies and interspecies communication, such as *comC* and *luxS*, respectively. Indeed, searching in silico yielded *luxS* of *P. gingivalis* (26), *A. actinomycetemcomitans* (48), and *S. pyogenes* (98), as well as *comC* of *S. mutans* (89).

Subtle regulation of gene expression in any organism within a community may lead to significant changes in the organism's ability to participate in community activities, such as use of community-formed metabolic end products as nutrients. Known progressive changes in species composition in natural communities with respect to time, nutrient availability, disease state, or other environmental conditions alert us to consider that a mutation in a relevant gene may cause only a subtle change that is critical in contributing to an organism's success in a community. Such subtle changes may be controlled by the regulation of multiple integrated pathways. Results from future research will build a better understanding of how small changes cause large shifts in population composition and metabolic output of mixed-species communities.

Furthermore, inactivation of a gene involved in mixed-species community formation may cause a subtle variation in an organism's phenotype only during critical transitions in population composition and have no effect on population composition before or after the transition. Dental plaque on human tooth enamel undergoes population transitions each day between oral hygiene regimens. Identifying genes that are critical for an organism's success in this environment may be possible not by screening mutants for absence of growth but rather by investigating subtle changes in an organism's participation in the community.

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